

Eosinophilia in Rheumatologic/Vascular Disorders



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KEYWORDS

- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Diffuse fasciitis with eosinophilia • Eosinophilic fasciitis
- Immunoglobulin G4-related disease • Eosinophilic myositis
- Eosinophilia-myalgia syndrome

KEY POINTS

- Rheumatologic and vascular conditions associated with peripheral or tissue eosinophilia are rare and can manifest with single-organ or systemic disease.
- The pathophysiology of rheumatologic and vascular conditions associated with peripheral or tissue eosinophilia remains largely unknown.
- A limited number of randomized controlled therapeutic trials have been performed in rheumatologic and vascular conditions associated with peripheral or tissue eosinophilia so that treatment is largely based on open-label and cohort studies.

INTRODUCTION

Eosinophilia in blood or tissue can be seen in many rheumatologic and vascular conditions (**Box 1**). Although this occurs as an uncommon but described feature in several diseases, for some entities eosinophilia seems to have a significant clinical and pathophysiologic role. When eosinophilia is seen in rheumatic or vascular conditions where this is not generally considered to be an integral part of the clinical picture, care should be taken to consider other causes of eosinophilia. These other causes can particularly include medications; allergic diseases; infections, especially parasitic

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Box 1
Rheumatologic or vascular conditions associated with tissue and blood eosinophilia
Common
EGPA (Churg-Strauss)
IgG4-related disease
DfE
Eosinophilia myalgia syndrome
EM
Less common
GPA (Wegener)
Polymyositis
Dermatomyositis
Inclusion body myositis
Rheumatoid arthritis
Systemic sclerosis
Sjögren syndrome
Systemic lupus erythematosus
Behçet disease

diseases; hematologic conditions; or the possibility of an alternative diagnosis. This article examines 5 rheumatologic and vascular conditions wherein peripheral blood or tissue eosinophilia is a prominent feature: eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), immunoglobulin G4 (IgG4)-related disease (IgG4RD), diffuse fasciitis with eosinophilia (DFE), eosinophilia-myalgia syndrome (EMS), and eosinophilic myositis (EM).

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS)

EGPA is a form of primary systemic vasculitis defined by the presence of eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, necrotizing vasculitis of the small to medium vessels, and an association with asthma and eosinophilia.¹ EGPA carries a wide spectrum of clinical manifestations and can be life-threatening. Although EGPA is considered within the family of antineutrophil cytoplasmic antibody (ANCA) -associated vasculitides, ANCA are found in a minority of patients and cannot confirm or exclude the diagnosis.

Epidemiology

Epidemiologic studies in EGPA have been difficult to perform. The incidence of EGPA has varied between 0 and 3.7 per million person-years with a prevalence of 2 to 22.3 million inhabitants.^{2,3} In studies of patients with asthma, the incidence of EGPA was reported to be 34.6 to 67 per million person-years.^{4,5} The mean age of diagnosis of EGPA is between 40 and 50 years with an equal occurrence in men and women.

Risk Factors

Two studies found an association between HLA and EGPA. HLA-DRB1*04 and HLA-DRB1*7 seemed to enhance disease risk, whereas HLA-DRB1*03 and HLA-DRB1*13

conferred protection.^{6,7} Single-nucleotide polymorphisms tagging the promoter haplotypes of IL10 gene (IL10–3575, IL10–1082, and IL10–592) were associated with EGPA, especially with ANCA-negative EGPA.⁸

The role of leukotriene receptor antagonists (LTRA) as a risk factor for the development of EGPA remains controversial. Following up on case reports, larger studies suggested an association between EGPA and LTRA.^{9,10} From a review of the US Food and Drug Administration (FDA) Adverse Event Reporting System database, LTRA were listed as suspect medications in 90% of the 181 reported cases of possible drug-induced EGPA.¹¹ Beyond a direct cause-effect relationship, one hypothesis has been that EGPA become unmasked when LTRA use allows asthmatic patients to taper glucocorticoids. It remains unclear to date whether LTRA have a direct role in the development of EGPA or if LTRA are a confounding factor in patients experiencing worsening asthma before the onset of other EGPA features.

Pathophysiology

The pathogenesis of EGPA is unknown, although eosinophils are thought to play a central role. Eosinophil cationic protein has been found in serum and tissues of patients with active EGPA and is thought to cause tissue damage.^{12,13} Interleukin (IL)-5 production is increased in patients with EGPA and is involved in the maturation and survival of eosinophils.^{14,15} Other Th2 cytokines, such as IL-4 and IL-13, have also been found to be increased in EGPA,^{15,16} leading to the hypothesis that this may be a Th2-driven disease. However, the histologic features of EGPA cannot be entirely explained by Th2 responses, and Th1 responses are thought to contribute to granuloma formation in EGPA.¹⁶ Other studies have demonstrated an increase in Th17 cells¹⁷ and reductions in T-regulatory cells.^{17,18}

Clinical Features and Diagnostic Investigation

In 1984, Lanham and colleagues¹⁹ described 3 phases of EGPA: a prodromal phase with allergic features, an eosinophilic phase characterized by peripheral and tissue eosinophilia, and a vasculitic phase with small to medium vessel vasculitis. Although recognition of these phases is conceptually helpful, they do not occur in all patients or always occur in sequence.

Long-standing sinonasal symptoms with allergic rhinitis and nasal polyps are common. Asthma is seen in more than 90% of patients^{19–22} and usually precedes the diagnosis of EGPA by 4 to 9 years. The asthma of EGPA typically begins in adulthood or becomes markedly worse in those with childhood onset. Parenchymal lung disease occurs in 37% to 63% and can manifest as fleeting peripheral pulmonary infiltrates or alveolar hemorrhage. Vasculitic features most commonly involve the peripheral nerve (motor or sensory mononeuritis multiplex) or skin (purpura, nodules, ulcerating lesions, livedo reticularis). Renal involvement is seen in 13% to 58% of patients. Although glomerulonephritis occurs less commonly than that in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), it has an identical histologic appearance in being a segmental, necrotizing, crescentic glomerulonephritis with few to no immune complexes (pauci-immune glomerulonephritis). Gastrointestinal disease in EGPA can be related to eosinophilic infiltration or vasculitis. Cardiac involvement (cardiomyopathy from myocarditis, pericarditis, endocarditis, valvulitis, coronary vasculitis) is important to recognize because it is the main cause of patient mortality and occurs in 12% to 58% of patients. An echocardiogram should be performed in all EGPA patients at the time of diagnosis and cardiac MRI may be useful in detecting cardiac involvement when this is suspected (**Fig. 1**). Patients with cardiac

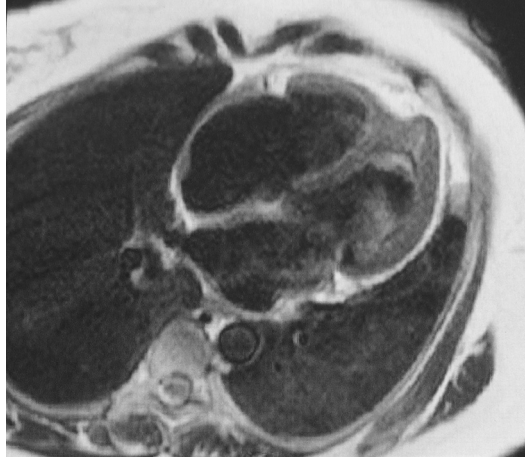


Fig. 1. Cardiac MRI demonstrating complications from heart involvement in EGPA (Churg-Strauss). This patient has endomyocardial fibrosis at the left ventricular apex with a large apical thrombus.

involvement tend to have a higher number of eosinophils and a negative ANCA,^{22,23} whereas more patients with a glomerulonephritis had a positive ANCA.^{24,25}

Diagnosing EGPA can be challenging because of the diversity of clinical features, the potential for these to be seen in other settings, and the frequent use of glucocorticoids for asthma, which will blunt peripheral eosinophilia. Central to the diagnosis of EGPA is the identification of vasculitic manifestations although this can be difficult to prove histologically. ANCA, which is more commonly myeloperoxidase ANCA, is seen in less than 40% of patients with EGPA and do not play a meaningful diagnostic role.

Differential Diagnosis

The 2 major categories within the differential diagnoses for EGPA are other eosinophilic disorders and diseases associated with small- to medium-vessel vasculitis (**Box 2**). The clinical manifestations of aspirin exacerbated respiratory disease (AERD) are asthma, chronic sinusitis, nasal polyps, and reaction to cyclooxygenase-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). Lung infiltrates or other systemic manifestations seen in EGPA are uncommon in AERD. Patients with chronic eosinophilic pneumonia exhibit pulmonary symptoms but do not have granuloma characteristic for EGPA in the lung histopathology and lack vasculitic features. Allergic bronchopulmonary aspergillosis causes asthma, lung infiltrates, rhinitis, sinusitis, and eosinophilia but does not affect other organ systems.

Hypereosinophilic syndrome (HES) is often the main diagnosis being differentiated from EGPA. It is defined by a combination of hypereosinophilia and organ damage or dysfunction attributable to hypereosinophilia, provided that other possible causes of organ damage are excluded.²⁶ The challenge in differentiating EGPA from HES lies in the similarity of organ involvement because of tissue infiltration of eosinophils in both conditions.²⁷ The presence of vasculitis is a key differentiating factor between HES and EGPA but can be difficult to confirm, and asthma is uncommon in HES. Certain types of HES are associated with cytogenetic abnormalities on bone marrow biopsy that are not seen in EGPA.

Box 2**Differential diagnosis for eosinophilic granulomatosis with polyangiitis (Churg-Strauss)***Eosinophilic disorders*

Hypereosinophilic syndrome

AERD

Eosinophilic pneumonia

Allergic bronchopulmonary aspergillosis

Gleich syndrome (episodic angioedema and eosinophilia)

Parasitic diseases

Hypersensitivity syndromes

Vasculitis

GPA (Wegener)

MPA

Cryoglobulinemic vasculitis

IgA vasculitis (Henoch-Schönlein)

Polyarteritis nodosa

The main vasculitic diseases that can have a similar appearance to EGPA are GPA and MPA, which can also affect the lungs, kidneys, skin, and peripheral nerve. However, asthma and peripheral eosinophilia are uncommon in GPA or MPA. Although sinus and lung disease can occur in both GPA and EGPA, GPA is associated with a far greater degree of tissue necrosis, which is not seen in EGPA.

Management

Treatment of EGPA is determined by the disease manifestations and their severity. Glucocorticoids are the foundation of treatment of EGPA, and for those patients with nonsevere EGPA, prednisone alone can be sufficient.²⁸ Asthma in particular is typically glucocorticoid responsive and also is the main factor that limits glucocorticoid tapering. Use of an additional immunosuppressive agent beyond glucocorticoids is based on the degree of disease severity. The 5-factor score (FFS) is a severity scoring system derived from patients with MPA, polyarteritis nodosa, and EGPA consisting of proteinuria greater than 1 g/L, creatinine greater than 1.58 mg/dL, cardiomyopathy, central nervous system disease, and gastrointestinal involvement.^{29,30} In one study of 64 patients, those with an FFS greater than or equal to 2 had an improved outcome when treated with cyclophosphamide,³¹ supporting that EGPA patients with organ- or life-threatening involvement should be treated with combined therapy. Cardiac involvement in particular should be treated with prednisone and cyclophosphamide given its risk of mortality and improvement in cardiac function with this treatment.

The treatment of severe EGPA has been extrapolated from that used in GPA and MPA. Although several EGPA studies have used intravenous cyclophosphamide, superiority over that of daily cyclophosphamide in EGPA has not been proven.³² The authors' approach in severe EGPA is to combine prednisone with daily cyclophosphamide, given for 3 to 6 months, after which time cyclophosphamide is stopped and switched

to a less toxic maintenance agent, usually consisting of either azathioprine or methotrexate.³³ Although there have been no controlled trials examining the use of these agents in EGPA, azathioprine or methotrexate combined with prednisone has also been used for less severe features, where the disease remains active or where there is an inability to taper prednisone to acceptable levels. Although this can provide benefit in those with vasculitic features, it has been less effective in those with predominantly sinus disease and asthma, although individual patient responses can be seen.

Experience with biologic agents in EGPA remains limited. The largest report of 41 patients with EGPA treated with rituximab showed improvement in 83% of patients.³⁴ Mepolizumab, an anti-IL-5 antibody, has been used for EGPA in a small number of patients with promising results.^{35,36}

Prognosis

The prognosis of EGPA has improved greatly.³⁷ Long-term outcomes in 2 treatment studies revealed a survival rate and disease-free survival rate of 98%/74% at 1 year, 94%/61% at 3 years, 92%/54% at 5 years, and 90%/51% at 7 years, respectively.³³ Another study of 383 patients with EGPA reported a 5-year survival of 89% and 10-year survival of 79%.²²

IMMUNOGLOBULIN G4-RELATED DISEASE

IgG4RD is a relatively newly defined systemic fibrotic inflammatory condition, which can involve multiple organ systems. Many manifestations of IgG4RD, such as autoimmune pancreatitis (AIP),³⁸ retroperitoneal fibrosis, Riedel thyroiditis, Küttner tumor, and Mikulicz disease (MD), were previously recognized as separate diseases but are now considered within the spectrum of IgG4RD. Histopathologic findings, including lymphoplasmacytic infiltrate with a high percentage of IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia and elevated IgG4 levels, have aided in the recognition and diagnosis of IgG4RD.^{39–42}

Epidemiology

The epidemiology of IgG4RD is yet to be investigated. A nationwide survey on the epidemiology of AIP in Japan revealed a prevalence of 2.2 per 100,000 and an incidence of 0.9 per 100,000 person-years.⁴³ In this study, the male-to-female ratio was 3.7:1 with disease occurring at a mean age of 63 years.

Risk Factors

Genetic risk factors for AIP have been explored in the Japanese population, where a possible link with HLA DRB1*0405-DQB1*0401 was suggested as well as an association with Fc receptor-like 3, KCNA3, and CTLA4 polymorphisms.^{44–47}

Pathophysiology

The pathogenesis of IgG4RD is unknown. IgG4 is considered noninflammatory, and it is currently unclear whether IgG4 plays a role in IgG4RD pathophysiology. Although eosinophils are often found on tissue biopsies in IgG4RD, current evidence does not support a pathogenic role. The expression of Th2 cytokines and regulatory cytokines were upregulated in affected tissues from patients with AIP as well as labial salivary gland specimens of MD.⁴⁸ Th2 is known to promote fibrosis by stimulating fibroblasts,⁴⁹ and one hypothesis is that Th2 predominance is the central pathway of fibrotic organ damage in IgG4RD. However, Th1 predominance was also reported

in 10 patients with IgG4-related sialadenitis,⁵⁰ and the numbers of regulatory T cells were also increased in peripheral blood from patients with AIP.

Clinical Features and Diagnostic Investigation

The range of clinical manifestations of IgG4RD continues to be actively described with features reported in almost every organ system where this can manifest as single-organ or multiorgan disease (**Box 3**).^{39,42}

Elevated serum IgG4 levels alone are not diagnostic because increased levels can be seen with patients with pancreatic cancer, and a normal serum IgG4 level does not rule out IgG4RD.^{51,52} In one study, the sensitivity of elevated serum IgG4 level greater than 135 mg/dL for the diagnosis of either definite or probable IgG4RD was 90%, whereas the specificity was 60%. If a higher cutoff of 270 mg/dL was used, the sensitivity was 35% and specificity was 91%.⁵³

The diagnosis of IgG4RD is based on its clinical features together with compatible histopathology, if feasible. Specific pathologic criteria for each organ have been proposed.^{40,54}

Differential Diagnosis

In patients with IgG4RD affecting a single organ, the differential diagnosis is tailored toward that specific site. Many systemic diseases can mimic the presentation of multiorgan IgG4RD.

For features such as aortitis and retroperitoneal fibrosis (**Fig. 2**), whereby access to tissue is difficult, evaluating for characteristic features of other diseases within the differential is important (**Box 4**). Takayasu arteritis is a granulomatous large-vessel vasculitis involving the aorta and its primary branches, which predominantly affects women 20 to 40 years of age. Giant cell arteritis is a granulomatous large- to medium-vessel vasculitis that has a predilection for branches of the carotid artery often presenting with cranial features and polymyalgia rheumatic, which predominantly affects people older than the age of 50. Erdheim-Chester disease (ECD) is a very rare multisystemic disease caused by the non-Langerhans form of histiocytosis that can manifest with circumferential periaortic sheathing of the thoracic or abdominal aorta. ECD is highly suggested by long bone uptake on bone scintigraphy and hairy kidney on abdominal CT scan.⁵⁵ The possibility of infectious aortitis needs to be carefully evaluated because atypical pathogens such as *Mycobacterium tuberculosis*, *Treponema pallidum*, or *Coxiella burnetii* can have a subacute course similar to IgG4RD. Lymphoma can present with retroperitoneal disease, and tissue biopsy should be considered wherever this is feasible in settings where lymphoma remains strongly in the differential.

Management

Glucocorticoids are the first-line treatment of IgGRD based on cohort studies. Cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine have been used for IgG4RD; however, the experience is limited.^{56,57} Small series including an open-label prospective trial have found rituximab to be effective in patients with refractory IgG4RD.^{58,59}

Prognosis

The prognosis of IgG4RD has not been well described. A multicenter analysis revealed 99% of patients with type 1 AIP treated with glucocorticoids achieved remission compared with 55% of those managed conservatively. More than one-third of these patients had at least one relapse with 67% of relapses occurring after glucocorticoid

Box 3

Clinical manifestations of immunoglobulin G4-related disease

Head, eyes, ears, nose, throat, and neck

Chronic sclerosing dacryoadenitis

Orbital pseudotumor

Orbital myositis

Dacryoadenitis

Submandibular and parotid gland enlargement

Scleritis

Nasolacrimal duct obstruction

Chronic sclerosing sialadenitis

Eosinophilic angiocentric fibrosis

Rhinitis

Nasal polyps

Chronic sinusitis

Otitis media with effusions

Eosinophilic otitis media

Sensorineural hearing loss

Inflammation of pharynx, hypopharynx

Tracheal inflammation

Vocal cord inflammation

Thyroid

Riedel thyroiditis

Fibrosing Hashimoto thyroiditis

Cardiovascular

Aortitis

Periaortitis

Constrictive pericarditis

Lungs and mediastinum

Inflammatory nodule

Thickening of the bronchovascular bundle

Interstitial pneumonitis

Sclerosing pleuritis

Fibrosing mediastinitis

Lymph nodes

Lymphadenopathy

Breast

Inflammatory pseudotumor

Sclerosing mastitis

Kidney/genitourinary

Tubulointerstitial nephritis
 Membranous nephropathy
 Low-density renal parenchymal lesions
 Chronic sclerosing pyelitis
 Prostatitis
 Orchitis
 Paratesticular pseudotumor
Abdomen
 Type I AIP
 Sclerosing cholangitis
 Sclerosing mesenteritis
 IgG4 hepatopathy
 Liver inflammatory pseudotumor
 Colonic pseudotumor
 Retroperitoneal fibrosis
Central nervous system
 Hypertrophic pachymeningitis
 Hypophysitis
 Hypopituitarism
Peripheral nervous system
 Perineural inflammation
Skin
 Skin nodules, papules
 Psoriasis-like lesions
 Erythematous maculopapular rashes
Systemic and other features
 Fever
 Weight loss
 Multifocal fibrosclerosis

Data from Brito-Zerón P, Ramos-Casals M, Bosch X, et al. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014;13(12):1203–10; and Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. *Lancet* 2014;385(9976):1460–71.

discontinuation.⁵⁷ Outcome may also be affected by a possible association between IgG4RD and malignancy.^{60,61}

DIFFUSE FASCIITIS WITH EOSINOPHILIA

DFE is an uncommon disorder characterized by thickened skin, peripheral eosinophilia, and hypergammaglobulinemia. Tissue eosinophilia is not essential for the diagnosis; hence, the preferred terminology is *diffuse fasciitis with eosinophilia* as opposed to *eosinophilic fasciitis*. The first 2 cases were described by Dr Shulman in 1974, such that DFE has also been called Shulman disease.⁶²

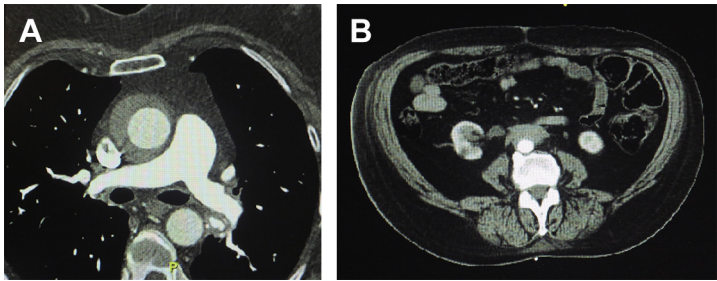


Fig. 2. Computed tomography showing periaortitis in a patient with IgG4-related disease. (A) Circumferential tissue thickening around the ascending aorta. (B) Heterogeneous region of soft tissue thickening just anterior to the infrarenal aorta.

Epidemiology

DFE is a very rare disorder and its epidemiology is unknown. A retrospective analysis of 52 cases revealed a slight female predominance (56%).⁶³ The mean age in this study was 40 to 50 years, although this has varied widely in other series.

Risk Factors

Multiple risk factors have been anecdotally linked to DFE, including physical stress, trauma, medications,^{64–70} chemicals,⁷¹ and infections.^{72–74} In one study of 52 cases

Box 4
Differential diagnosis for aortitis and retroperitoneal fibrosis manifestations of immunoglobulin G4-related disease
<i>Aortitis</i>
Primary vasculitic diseases
• Giant cell arteritis
• Takayasu arteritis
• Cogan syndrome
• Behçet disease
ECD
Sarcoidosis
Ankylosing spondylitis
Relapsing polychondritis
Infectious aortitis
<i>Retroperitoneal fibrosis</i>
Idiopathic retroperitoneal fibrosis
Lymphoma
Sarcoma
Tuberculosis
Retroperitoneal fibromatosis (desmoid tumors)
Methysergide-induced retroperitoneal fibrosis

of DFE, 5 patients (9%) had hematologic disorders including 2 patients with thrombocytopenia, one with myelomonocytic leukemia, one with chronic lymphocytic leukemia, and one with evolving myeloproliferative disorder.⁶³ Associations with other hematological disorders have been reported anecdotally.^{75–87}

Pathophysiology

The pathophysiology of DFE remains to be elucidated, but limited data suggest immune dysregulation. The inflammatory cells in tissue histopathology⁸⁸ consist of eosinophils, CD8+ lymphocytes, and macrophages, which have been thought to cause tissue damage in DFE.⁸⁹ T cells in DFE stimulated by T-cell activator phytohemagglutinin produce more Th2 cytokines as well as Th1 cytokines compared with healthy controls.⁹⁰ The serum and tissue levels of tissue inhibitor of metalloproteinase-1 was elevated in DFE,⁹¹ which was implicated as a potent stimulator of systemic sclerosis (SSc) fibroblasts.

Clinical Features and Diagnostic Investigation

DFE is characterized by acute or subacute symmetric swelling, erythema, and stiffness of the distal extremities sometimes with pitting edema. These early changes evolve into woody induration, and eventually DFE patients exhibit a characteristic appearance of skin puckering (peau d'orange appearance) and depressed veins (groove sign) (Fig. 3).^{92,93} The level of inflammation and fibrosis is deep in the subcutis. Hence, the epidermis is normal on examination, but there is a deeper level of induration (subcutaneous rather than dermal as seen in SSc). DFE predominantly involves the extremities and can cause joint contractures and tendon retractions. In one report of 52 patients, all patients had extremity involvement, with other affected areas, including the abdomen (23%), chest (17%), back (6%), buttocks (6%), and face/neck (6%).⁶³ Polyarthritides can be seen in up to 40% of patients⁶³ and carpal tunnel syndrome in up to 23% of patients.⁶³

The diagnosis of DFE is based on clinical features and histopathology on a full-thickness biopsy of an affected area (including skin, subcutaneous fat, and fascia). A punch biopsy is not adequate because it will miss the fascia, the main site of pathologic abnormality in DFE (Fig. 4). Pinal-Fernandez and colleagues⁹³ proposed diagnostic criteria of DFE requiring the presence of both major criteria, or one major criterion plus 2 minor criteria, following the exclusion of SSc. Major criteria include (1) swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetric or nonsymmetric, diffuse (extremities, trunk, and abdomen), or localized (extremities); (2) fascial thickening with accumulation of lymphocytes and

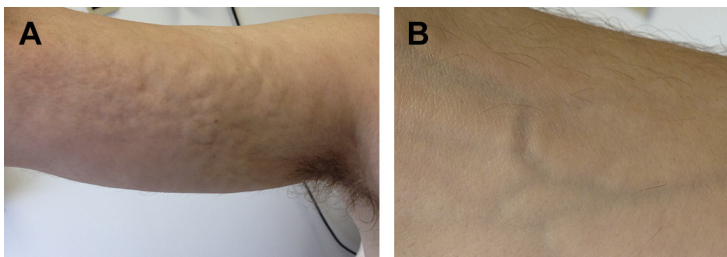


Fig. 3. Clinical findings in a patient with DFE. (A) Peau d'orange of the upper extremity. (B) Groove sign representing depressed veins.

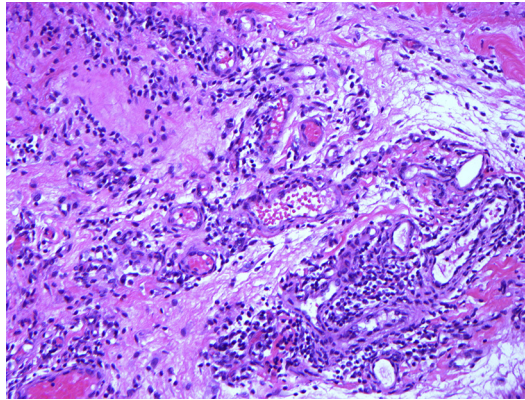


Fig. 4. Histologic section shows a prominent chronic inflammatory cell infiltrate primarily involving the deep fascia. There is no evidence of necrotizing vasculitis or granulomatous inflammation. These findings are consistent with chronic fasciitis as is seen in DFE (Hematoxylin and eosin, $\times 200$).

macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin). Minor criteria include (1) eosinophilia greater than $0.5 \times 10^9/L$; (2) hypergammaglobulinemia greater than 1.5 g/L; (3) muscle weakness or elevated aldolase levels; (4) groove sign or peau d'orange; (5) hyperintense fascia on MRI T2-weighted images.

Differential Diagnosis

The major differential diagnoses of DFE include SSc and its mimics. In a retrospective study of 52 patients with DFE, only one patient had Raynaud phenomenon,⁶³ whereas more than 90% of patients with SSc have Raynaud phenomenon. Fingers, feet, and face are typically not affected in DFE compared with SSc. Nailfold capillaries are usually normal in DFE, whereas abnormal nailfold capillaries tend to be seen in SSc.⁹⁴ Visceral involvement is uncommon in DFE, whereas SSc can affect the pulmonary, cardiovascular, gastrointestinal, and renal systems. Antinuclear antibodies (ANA) can be found in 85% to 90% of patients with SSc, but in a study of 52 DFE patients, only 3 (6%) were positive for ANA.⁶³ Other entities including chronic graft-versus-host disease, nephrogenic systemic fibrosis, scleromyxedema, and scleredema can be differentiated from DFE based on clinical features and skin biopsy.⁹⁵

The differential diagnoses for skin thickening with eosinophilia include EMS and toxic oil syndrome. Pneumonitis or neuropathy can be seen in EMS.^{96,97} Toxic oil syndrome was associated with adulterated rapeseed oil in an endemic outbreak in Spain during the 1980s. Clinical manifestations include dyspnea, myalgia, arthralgia, and neuropathy with eosinophilia and elevation of serum creatine kinase.^{97,98}

Management

The treatment approach to DFE has been based on case reports and cohort series. Spontaneous recovery has been noted, but most reported patients were treated with immunosuppressive agents. In a series of 52 patients, 34 were initially treated with prednisone 40 to 60 mg daily, which resulted in complete resolution in 15%, partial response ($>25\%$ improvement) in 59%, and poor response in 27%. In 5 patients who received no treatment, resolution occurred in 40%, more than 50% improvement

in 40%, and no improvement in 20%.⁶³ In a retrospective study of 34 patients with DFE where the mean initial dose of prednisone was 0.77 mg/kg, 44% received an additional immunosuppressive agent due to an inadequate clinical response (methotrexate 86%, azathioprine 14%).⁹⁹ Overall, 69% of patients achieved a complete remission, with 19% experiencing remission with disability, and 12% having treatment failure. Fifteen patients (47%) were treated with methylprednisolone pulses before prednisone and were found to require a second immunosuppressive less frequently (20% vs 65%, $P = .02$) and more readily achieve complete remission (87% vs 53%, $P = .06$).⁹⁹ Cyclosporine, cyclophosphamide, hydroxychloroquine, and sulfasalazine have been used in small case series. There has been only anecdotal experience with infliximab,^{100–102} etanercept,¹⁰³ and rituximab.¹⁰⁴

Prognosis

The prognosis of patients with DFE is not well documented. From a retrospective study, predictors for poor outcomes included diagnosis delay greater than 6 months and absence of methylprednisolone pulses at treatment initiation.⁹⁹

EOSINOPHILIA-MYALGIA SYNDROME

EMS first emerged as a disease entity in 1989 with a new epidemic in the United States of a multisystem disease characterized by severe muscle pain and profound eosinophilia.¹⁰⁵ Case control studies in Minnesota, Oregon, and New Mexico determined an association between antecedent tryptophan consumption and EMS.^{106,107}

Epidemiology

In 1989, more than 1500 cases of EMS related to tryptophan occurred in the United States that resulted in 36 deaths by 1991.¹⁰⁸ After the FDA banned the sale of products containing tryptophan, the incidence of EMS declined rapidly. An isolated case associated with L-tryptophan was reported in 2005.¹⁰⁹

Risk Factors

Tryptophan was identified as a causative agent for EMS in epidemiologic studies.^{106,107} Further investigation revealed a strong association with the consumption of L-tryptophan produced by one company.^{110,111} More than 60 minor impurities were detected in this company's products, 6 of which were reported to be associated with EMS.¹¹² Lewis rats treated with one of these impurities, 1,1'-ethylidenebis (tryptophan) (EBT) or case-associated L-tryptophan, developed myofascial thickening similar to human EMS, but Lewis rats treated with L-tryptophan without EBT also showed mild myofascial thickening.¹¹³ Another impurity, 3-(phenylamino) alanine, shares chemical properties with 3-(M-phenylamino)-1,2-propanediol, which was implicated as a causative agent of toxic oil syndrome in Spain in 1981.¹¹⁴

Pathophysiology

The pathophysiology of EMS remains unclear. The cellular immune response and cytokines/growth factors, such as IL-2, IL-4, IL-5, interferon- γ , granulocyte-macrophage colony-stimulating factor, and transforming growth factor- β , have been implicated in the pathophysiology of EMS.¹¹⁵

Clinical Features and Diagnostic Investigation

The cardinal features of EMS are severe muscle pain and peripheral eosinophilia. Criteria established by the US Centers for Disease Control and Prevention include eosinophil count greater than or equal to 1.0×10^9 cells/L, generalized myalgia severe enough to interfere with normal daily activities, and no infectious or neoplastic condition that could account for these findings. Cough or dyspnea can be seen in up to 60% of patients and chest radiograph abnormality was seen in approximately 20% of the cases. Neuropathy can be seen in up to 30% of patients and was more common in those with a fatal outcome. Other common manifestations include fever (35%), rash (60%), arthralgia (70%), peripheral edema (60%), and thickened skin (35%).¹⁰⁸

The diagnosis of EMS is based on a compatible clinical presentation, peripheral blood eosinophilia, and histopathology, which reveals perimyositis with inflammatory cells predominantly consisting of mononuclear cells and eosinophils.¹¹⁶

Differential Diagnosis

The differential diagnosis of EMS is similar to that of DFE as listed previously. The clinical differences between DFE and EMS can be subtle or none and they are mainly differentiated by prior exposure to tryptophan that occurs in EMS.^{117–119} Severe myalgias, neuropathy, respiratory symptoms, and cognitive impairment are not seen in DFE.

Management

Treatment of EMS beyond discontinuation of the offending substance is not well established. Glucocorticoids or other immunosuppressive agents have been used.

Prognosis

A report of 205 patients with EMS with 18- to 24-month follow-up after disease onset showed improvement in myalgias (67%), respiratory symptoms (74%), muscle weakness (60%), arthralgias (66%), fever (88%), swelling (80%), and paresthesia (51%). Prednisone was used in most patients with full improvement by physician's evaluation in 19% of patients and partial improvement in 60%.¹²⁰

EOSINOPHILIC MYOSITIS

EM is a very rare disease and contains a diverse group of disorders. EM includes 3 major subtypes: eosinophilic polymyositis (EP), eosinophilic perimyositis (EPM), and focal eosinophilic myositis (FEM). These disorders have only been reported in case reports or small case series.

Epidemiology

No population-based epidemiologic data are available. In one review of 20 men and 11 women, the mean age was 47 years, consisting of 13 patients with EPM, 7 with EP, 10 with FEM, and 1 patient with cyclic EM (unclassified).¹²¹

Risk Factors

No major risk factors for EM have been identified because of its rarity. Heavy alcohol use was suggested as a trigger for FEM in case reports^{122,123} as well as trauma.¹²⁴

Pathophysiology

The pathophysiology of EM is unknown because of its rarity. It is generally thought that eosinophils and cytotoxic proteins released by eosinophils as well as cytotoxic T cells

elicit muscular injury.¹²⁵ Muscle biopsy specimens from 3 patients with EP revealed elevated IL-5 messenger RNA levels, suggesting that local expression of IL-5 led to an accumulation of eosinophils in the muscle.¹²⁶

Clinical Features and Diagnostic Investigation

Diagnostic criteria for FEM, EPM, and EM have been proposed¹²⁷ (**Box 5**). These criteria are based on the main clinical, laboratory, and histologic features that have been described in these diseases.^{121–129}

Box 5

Proposed diagnostic criteria for focal eosinophilic myositis, eosinophilic polymyositis, and eosinophilic perimyositis

Proposed diagnostic criteria for focal eosinophilic myositis

Deep vein thrombosis, cellulitis, and parasitic infections must be excluded to apply these criteria.

To fulfill the criteria, 2 major criteria or one major criterion and all minor criteria are required.

Major criteria:

1. Pain and calf swelling (other muscles can be affected)
2. Deep mononuclear cell infiltration (eosinophilic or not), with muscle fiber invasion and necrosis on muscle biopsy

Minor criteria:

1. Elevated serum levels of creatine kinase and aldolase (2- to 10-fold)
2. MRI or electromyographic evidence of focal myositis
3. Absence of systemic illness
4. Eosinophilia greater than $0.5 \times 10^9/L$

Proposed diagnostic criteria for eosinophilic polymyositis

To fulfill the criteria, presence of both major criteria or one major criterion and 2 minor criteria are required.

Exclusion: Hypereosinophilic syndrome, T-cell clonality, dermatomyositis, vasculitis (EGPA [Churg-Strauss]), drugs, limb girdle muscle disease (Becker muscular dystrophy, calpainopathy, and sarcoglycanopathy), and parasitic infections must be excluded.

Major criteria:

1. Proximal weakness exists, affecting limb-girdle muscles, sometimes severe.
2. Widespread deep infiltration of eosinophils into muscle, with eosinophilic cuffing on histology study. Myonecrosis and endomysial inflammation usually present. In the absence of eosinophil infiltration, major basic protein deposition should be demonstrated by specific immunostaining.

Minor criteria:

1. Elevated serum levels of creatine kinase and aldolase (usually high, >10 upper limit of normal)
2. Eosinophilia greater than $0.5 \times 10^9/L$
3. Systemic illness with frequent cardiac involvement
4. Corticosteroids are needed

Proposed diagnostic criteria for eosinophilic perimyositis

Toxic oil syndrome, myalgia-eosinophilia, exposure to other inorganic or organic substances should be excluded.

Presence of both major criteria and major criterion number 2 plus 2 minor criteria are required for the diagnosis.

Major criteria:

1. Myalgia, proximal mild weakness
2. Eosinophilic infiltrate confined to fascia and superficial perimysium, absence of myofiber necrosis

Minor criteria:

1. Absence of systemic manifestations
2. Normal creatinine kinase, aldolase levels slightly elevated (less than 2- to 3-fold of upper limit of normal).
3. Eosinophilia greater than $0.5 \times 10^9/L$

Adapted from Selva-O'Callaghan A, Trallero-Araguas E, Grau JM. Eosinophilic myositis: an updated review. Autoimmun Rev 2014;13(4-5):375-8.

Management

No treatment trials have been conducted in EM because of its rarity and lack of consensus criteria such that treatment is based on case reports. FEM can improve spontaneously, but rapid response to glucocorticoids has been reported. Some patients with FEM were treated with NSAIDs. EPM usually responds to glucocorticoids but often long-term treatment is necessary. EP typically spontaneously resolves but glucocorticoids or NSAIDs have been used with success, although relapses were noted.^{121,124,128,130}

Differential Diagnosis

Evaluation for secondary causes of EM is necessary to explore potential parasitic infestations, such as trichinosis, cysticercosis, sarcocystis, or toxoplasmosis,¹³¹⁻¹³⁵ or a systemic eosinophilic disorder that can cause EM. HES can mimic EPM, especially in the setting of myocardial involvement. However, in a retrospective multicenter study of 188 patients with HES, only one had myositis and 9 had myalgias as the initial presentation.²⁷ In a retrospective study of 383 patients with EGPA, 39% had myalgias at diagnosis²²; however, true myositis is rare.¹³⁶ Recently, cases of EM associated with muscular dystrophies have been reported.¹³⁷⁻¹⁴⁴ Major differential diagnoses of FEM include deep vein thrombosis, inflammatory pseudotumor, and parasitic infestations. Differential diagnoses of EP include EMS or toxic oil syndrome.

Prognosis

Prognosis of this diverse disease group is unknown.

SUMMARY

The rheumatologic and vascular disorders associated with eosinophilia represent an uncommon but important group of disease entities. Despite their rarity, increasing knowledge has been accumulated in recent years and novel therapies are being explored, particularly in those diseases whereby the consensus for their classification/diagnostic criteria have been established and wherein collaborative work has

been performed. Establishment of disease definitions is necessary in some of rheumatologic and vascular disorders associated with eosinophilia to promote more accurate and detailed description of the diseases and to meet unmet needs; this is critically important given that multicenter collaboration will play an essential role to further investigate these rare disease entities.

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